Docket No.: PC-0025 CIP

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1646

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By: _____ Printed: Jeannie G. Labra

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Michael G. Walker

Title: ANKYRIN REPEAT DOMAIN 2 PROTEIN VARIANT

Serial No.:	09/758,593	Filing Date:	January 10, 2001
Examiner:	Li, R.	Group Art Unit:	1646

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed January 22, 2004, and received by the USPTO on January 26, 2004, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the **$ 330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1-12 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Genomics, Inc., (now Incyte Corporation) (Reel 011909, Frame 0532) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related

appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1-12.
Claims allowed:	(none).
Claims canceled:	Claims 13-20.
Claims withdrawn:	(none).
Claims on Appeal:	Claims 1-12 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

An amendment after Final Rejection was filed in accordance with the Examiner's rejections and suggestions in order to place the application in better condition for allowance or appeal. For purposes of appeal, the proposed amendment will be entered. See Advisory Action, mailed March 4, 2004.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to polynucleotides encoding an Ankyrin Repeat Domain 2 protein variant (Ankrd2V:SEQ ID NO:1) and a a naturally occurring variant of the amino acid sequence of SEQ ID NO:1 having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1. The invention is further directed to the polynucleotide sequence of SEQ ID NO:2 encoding SEQ ID NO:1, a specific fragment of SEQ ID NO:2 selected from SEQ ID NOs:4-6, and a variant of SEQ ID NO:2 selected from SEQ ID NOs:7-10. Nucleic acids encoding the Ankrd2V of the present invention were first identified as a cardiac muscle-associated gene through the exhibition of a strong association, or coexpression, with known genes that are specifically cardiac muscle-associated. See specification, at page 9, line 33 through page 10, line 14. Northern analysis further showed the expression of the transcript encoding Ankrd2V in musculoskeletal tissues, with a particularly high abundance in a patient with clear cell sarcoma (MUSCNOT10). See specification, at page 10, lines 23-29.

Ankrd2V is identified as skeletal muscle protein by a high level of sequence identity (88%) with two ankyrin-repeat mouse proteins, Mus musculus Ankrd2 (g9501360), and M. musculus skeletal muscle and cardiac protein (SMCP; g5420272), SEQ ID NOs:11-12, respectively, and by the conservation in Ankrd2V of various structural and functional motifs common to the known proteins. See specification, at page 11, lines 5-14. The claimed polynucleotides are therefore asserted to be useful in the diagnosis and treatment of muscle disorders such as muscle hypertrophy and clear cell sarcoma.

(6) ISSUES

1. Whether claims 1-12 directed to Ankrd2V encoding polynucleotide sequences, and fragments and variants thereof meet the enablement requirements of 35 U.S.C. §112, first paragraph. In particular, whether the claimed variants and fragments of SEQ ID NO:2 and variants of SEQ ID NO:1 are sufficiently enabled that the skilled artisan would know how to make and/or use them.

2. Whether claims 1 and 3-12 are in accordance with the written description requirements of 35 U.S.C. §112, first paragraph. In particular, whether an isolated cDNA comprising a nucleic acid sequence encoding a naturally occurring variant of SEQ ID NO:1 having at least 90% identity to the amino acid sequence of SEQ ID NO:1 is sufficiently described that one skilled in the art would recognize applicants possession of said variants at the time the application was filed

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims are grouped together.

As to Issue 2

Claims 1 and 3-12 are grouped together. Claim 2 stands alone

(8) APPELLANTS' ARGUMENTS

Claims 1-12 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for one skilled in the art to use the invention commensurate with the scope of the claims. The rejection alleges in particular that:

- while the claimed fragments of SEQ ID NO:2 may be used as a probe for the diagnosis of clear cell sarcoma, the claimed variants may not be used as a probe for the diagnosis of disease conditions associated with differential expression of Ankrd2v because determining the specificity of hybridization is empirical by nature and the effect of mismatches is unpredictable, as taught by Wallace et al. (1987) and Sambrook et al. (1989).
- The specification also fails to provide sufficient information on how to produce naturally occurring variants of SEQ ID NO:1 having at least 90% identity to SEQ ID NO:1. There is no sufficient guidance or working examples on how to make and us the variants in producing transgenic cell lines or organisms which model human disorders. Regarding thte sequences recited in claim 2, the specifcation is silent on how to use these variants of a small portion of SEQ ID NO:2 to produce transgenic cell lines or organisms which model a human disorder, in particular, human clear cell sarcoma. Thus, one skilled in the art would not be able to practice the invention without undue experimentation.
- In addition, claim 6 also remains rejected because of its recitation of "A vector", which was suggested to be replaced by "An expression vector" in claim 4 to overcome this part of the rejection.

The rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph for lack of enablement is improper, as the inventions of those claims are sufficiently enabled through the described utilities that one skilled in the art would know how to make and/or use them

Claim 4 has been amended to recite "An expression vector" as the Examiner has suggested. Applicants disagree that one skilled in the art would not know how to use the claimed polynucleotides as probes, for example, for identifying naturally occurring molecules encoding Ankrd2V, allelic variants, or related molecules (specification, at p. 13, lines 22-26); in arrays to monitor large number of genes simultaneously and to identify genetic variants and mutations (specification, at p. 14, lines 16-24); and for chromosomal mapping (specification, at p. 14, lines 25-29). In particular, applicants disagree that the art, as evidenced by Wallace et al. and

Sambrook et al., cited by the Examiner, support an allegation that the effect of mismatches on the specificity of hybridization of polynucleotide seqeuences, such as those claimed in the instant application, are "unpredictable" to the extent that the skilled artisan would not know how to use them in the hyridization assays described in the specification without undue experimentation. Indeed the Wallace and Sambrook references cited by the Examiner are both laboratory manuals describing procedures that are now routine in the art.

On the contrary, the overall teachings of Sambrook et al (1989) in the reference cited by the Examiner, support applicants position as described in the specification at page 13, line 22 through page 145, line 15, that the specificity of hybridization is highly predictable based the various conditions that may be modified to control the specificity of hybridization. Such procedures are routine in the art and do not constitute "undue experimentation" The single page in Sambrook cited by the Examiner merely discusses the effect of mismatches in base pairing on one parameter of hybridization specificity, i.e., melting temperature (Tm). While the reference does recite that the effect of these mismatches on Tm can be determined empirically and refers to procedures in the manual for determining these effects, the procedures are routine in the art. The Wallace article (1987) specifically discusses issues associated with the specificity of oligonucleotide probes based on parameters such as oligonucleotide length and G + C content, and discusses methods similar to those described in Sambrook for determining the effects of these parameters on hybridization specificity, again using methods that are routine in the art.

Applicants therefore submit that the skilled artisan would know how to use the claimed polynucleotides in hybridization assays to distinguish between Ankrd2V encoding polynucleotides and related molecules in a sample, in arrays to monitor large number of genes simultaneously and to identify genetic variants and mutations, and for chromosomal mapping without undue experimentation using procedures that are routine in the art for regulating the degree of specificity in the hybridization assays. Withdrawal of the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph is therefore requested.

Claims 1 and 3-12 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection alleges in particular that:

- claim 1(b) recites an isolated cDNA comprising a nucleic acid sequence encoding a naturally occurring variant of SEQ ID NO:1 having at least 90% identity to the amino acid sequence of SEQ ID NO:1, and there is no disclosure of such variants. The Examiner further stated that the claim is drawn to a genus of nucleic acids that is defined only by partial sequence identity to SEQ ID NO:1, not by complete chemical structure as Applicants argued. The claims do not require that the nucleic acids possess any particular biological activity nor any particular conserved structure, or disclosed distinguishing feature. The specification further fails to provide representative examples of such variants and methods of making such variants.
- Accordingly, the Examiner stated, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The Examiner then cited various case law in support of his position, including *Vas-Cath Inc v. Mahurkar, Fiers v. Revel,* and *Amgen v. Chugai Pharmaceutical Co.*

The rejection of claims 1 and 3-12 under 35 U.S.C. § 112, first paragraph is improper, as the inventions of those claims are sufficiently described in terms of chemical and physical structure that one skilled in the art would recognize applicants possession of them at the time the application was filed.

Applicants have argued that the requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law as well as by the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001. Applicants simply disagree with the Examiner's interpretation of these requirements. For example, *Vas-Cath Inc v. Mahurkar* states:

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

The Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., **complete or partial structure, other physical and/or chemical properties,** functional characteristics when coupled with a known or disclosed correlation between function and structure, **or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.** If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met (emphasis added).

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the application (see, for example, page 3, lines 24-26). Variants of SEQ ID NO:1 are described, for example, at page 4, lines 22-23, where, in particular, a variant having at least 85% amino acid sequence similarity to SEQ ID NO:1 is described. Incyte clones in which the nucleic acids encoding the human Ankrd2V were first identified and libraries from which those clones were isolated are described, for example, at page 10, lines 18-22 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, on page 10, line 30 through page 11, line 14. Given SEQ ID NO:1, and the various chemical and structural features described for SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 having 90% sequence identity to SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Office Action has further asserted that the claims are not supported by an adequate written description because:

> The claims do not require that the nucleic acids possess any particular biological activity (claims 1), nor any particular conserved structure, or other disclosed distinguishing feature (claim 1(b)). Thus the claims are drawn to a genus of nucleic acids that is defined only by partial sequence identity.
>
> (page 9 of the Office Action mailed 5/20/2003)

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides or polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. An isolated cDNA ... comprising a nucleic acid sequence encoding a protein selected from the group consisting of:...b) a naturally-occurring variant of the amino acid sequence of SEQ ID NO:1 having at least 90% identity to the sequence of SEQ ID NO:1...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is highly variant

Furthermore, the claims at issue do not describe a genus which could be characterized as highly variant. Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the reference cited at page 29 of the specification by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to ankyrin repeat domain 2 proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as ankyrin repeat domain 2 proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 329 amino acid residues). This variation is far less than that of all potential ankyrin repeat domain 2 proteins related to SEQ ID NO:1, i.e., those ankyrin repeat domain 2 proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of April 26, 1999. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants encoding SEQ ID NO:1 at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by claim 1 is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

Applicants submit that one skilled in the art would clearly recognize applicants possession of the claimed variants of SEQ ID NO:1 based on the extensive chemical and structural features described for SEQ ID NO:1, and withdrawal of the rejection of claims 1 and 3-12 under 35 U.S.C.§ 112, first paragraph for lack of adequate written description is therefore requested.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,

INCYTE CORPORATION

Date: March 19, 2002

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Enclosures:

1. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998)

APPENDIX - CLAIMS ON APPEAL

1. An isolated cDNA, or the complement thereof, comprising a nucleic acid sequence encoding a protein selected from the group consisting of:
   a) an amino acid sequence of SEQ ID NO:1; and
   b) a naturally occurring variant of the amino acid sequence of SEQ ID NO:1 having at least 90% identity to the amino acid sequence of SEQ ID NO:1.

2. An isolated cDNA comprising a nucleic acid sequence selected from:
   a) SEQ ID NO:2 or the complement thereof;
   b) a fragment of SEQ ID NO:2 selected from SEQ ID NOs 4-6 or the complements thereof; and
   c) a variant of SEQ ID NO:2 selected from SEQ ID NOs:7-10.

3. A composition comprising the cDNA or the complement of the cDNA of claim 1 and a labeling moiety.

4. An expression vector comprising the cDNA of claim 1.

5. An isolated host cell comprising the vector of claim 4.

6. A method for using a cDNA to produce a protein, the method comprising:
   a) culturing the host cell of claim 5 under conditions for protein expression; and
   b) recovering the protein from the host cell culture.

7. A method for using a cDNA to detect expression of a nucleic acid in a sample comprising:
   a) hybridizing the composition of claim 3 to nucleic acids of the sample, thereby forming hybridization complexes; and
   b) comparing hybridization complex formation with a standard, wherein the comparison indicates expression of the cDNA in the sample.

8. The method of claim 7 further comprising amplifying the nucleic acids of the sample prior to hybridization.

9. The method of claim 7 wherein the composition is attached to a substrate.

10. The method of claim 7 wherein increased expression of the cDNA in the sample when compared with a standard of normal tissue is diagnostic of clear cell sarcoma.

11. A method of using a cDNA to screen a plurality of molecules or compounds for a molecule or compound that specifically binds the cDNA, the method comprising:
   a) combining the cDNA of claim 1 with a plurality of molecules or compounds under conditions to allow specific binding; and

b) detecting specific binding, thereby identifying a molecule or compound which specifically binds the cDNA.

12. The method of claim 11 wherein the molecules or compounds are selected from DNA molecules, RNA molecules, artificial chromosome constructions, peptides, transcription factors, and repressors.